7.61-7.51 (m, 2H), 7.40 (t, J=8 Hz, 1H), 7.09 (dd, J=1, 7.5 Hz, 1H), 3.2 (br s, 4H), 2.75 (br s, 4H), 2.46 (s, 3H), 0.39 (s with Sn coupling of 55.0 and 52.5 Hz, 9H).

Preparation 4

[0375] 8-Bromo-2-(dibenzylamino)-naphthalene

[0376] A mixture of dibenzylamine (70.8 mL, 0.368 mol), 8-bromo-2-tetralone (82.86 g, 0.368 mol, U.S. Pat. No. 4,897,405 A), dry toluene (1000 mL), and p-toluenesulfonic acid (0.83 g, 4.36 mmol) was refluxed 2 days with azeotropic removal of water. Most of the toluene was distilled away from the reaction and the residual material was dried in vacuo about 12 hours. The crude enamine was obtained as an orange oil and was used directly in the next step. ^{1}H NMR a 7.41-7.17 (m, 13H), 6.97 (d, J=7.3 Hz, 1H), 6.72 (t, J=7.6 Hz, 1H), 5.83 (s, 1H), 4.54 (s, 4H), 2.86 (t, J=7.8 Hz, 2H), 2.55 (dd, J=8.5, 6.6 Hz, 2H).

[0377] The enamine from the above reaction was dissolved in tetrahydrofuran (2000 mL) and chilled to 0° C. Chloranil (90.48 g, 0.368 mol) was added in portions over 10 minutes. The black solution was stirred 1.45 hours at 0° C., then the solvent was removed at reduced pressure. The residue was taken up in methylene chloride (750 mL) and filtered through celite to remove an insoluble yellow material (discarded). Saturated sodium carbonate (600 mL) was added to the filtrate and the two phase mixture was vigorously stirred 15 minutes. The mixture was again filtered through celite to remove a greenish solid (discarded). The phases were separated from the filtrate and the organic layer was washed with saturated sodium carbonate and then brine. The solution was dried over calcium sulfate and concentrated onto silica gel and applied to a flash chromatography column (4x4 inches silica gel). Elution proceeded as follows: hexane (500 m; nil); 5% ether/hexane (2 L, nil); 5% ether/hexane (12 L, unweighed orange oil product). The oil was triturated with 50% ether:hexane (500 mL) to yield the tan product, 8-bromo-2-(dibenzylamino)-naphthalene (72.15 9). The residues from the trituration were rechromatographed as above to afford an additional 18.95 g of product. The combined yield was 91.1 g, 61%. mp 102.5-103° C.; ^{1}H NMR δ 7.64-7.60 (m, 3H), 7.37-7.24 (m, 11H), 7.13 (dd, J=9, 2.5 Hz, 1H), 7.00 (t, J=7.8 Hz, 1H), 4.80 (s, 4H). Analysis calculated for $C_{24}H_{20}BrN$: C, 71.65; H. 5.01; N, 3.48. Found: C, 71.24; H, 4.65; N. 3.49.

Preparation 5

[0378] 2-Chloro-3-nitropyridine-N-oxide

[0379] 2-Chloro-3-nitropyridine (0.69 g, 4.35 mmol) was chilled to 0° C. and trifluoroacetic acid (9 mL) was slowly added followed by 30% hydrogen peroxide (1 mL). The solution was warmed to 70° C. for 1.5 hours, cooled to 0° C. and excess peroxide was decomposed by dropwise addition of dimethylsulfide (1 mL) and stirring 0.5 hours. The reaction was concentrated at reduced pressure onto silica gel and flash chromatographed (1x3 inches). Elution proceeded as follows: 50% ethyl acetate/hexane (175 mL), nil; 75% ethyl acetate/hexane (175 mL), 0.589 g (77%) of 2-chloro-4-nitropyridine-N-oxide as an orange solid suitable for use without further purification. A sample recrystallized from ethyl acetate/hexane had mp 98-100° C. Analysis calculated for $C_5H_3ClN_2O_3$: C, 34.41; H, 1.73; N. 16.05. Found: C, 34.75; H, 1.67; N. 15.80.

Preparation 6

[0380] 5-Trimethylstannylpyrimidine

[0381] A mixture of 5-bromopyrimidine (4.00 g, 25.16 mmol), hexamethylditin (9.06 g, 27.67 mmol), lithium chloride (1.27 g, 30.19 mmol), tetrakis(triphenylphosphine) palladium (1.13 g, 0.981 mmol), 2,6-di-tert-butyl-4-methylphenol (approximately 0.01 g), and dioxane (45 mL) was heated at reflux under nitrogen for 7 hours. The resulting mixture was concentrated via evaporation under reduced pressure, and the residue was column chromatographed using silica gel (approximately 200 g) and elution with ethyl acetate/hexanes [1:1] to afford the title compound (4.75 g, 19.6 mmol, 78%) as a clear, colorless liquid: R_f=0.6 in ethyl acetate/hexanes [1:1]; ^{1}H NMR ($CDCl_3$) δ 9.11 (s, 1H), 8.70 (s, 2H), 0.38 (s, 9H); ^{13}C NMR ($CDCl_3$) 6162.8, 158.5, 134.4, -9.6.

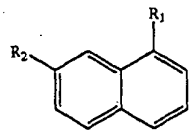
Preparation 7

[0382] 5-Cyano-3-trimethylstannylpyridine

[0383] A mixture of 3-bromo-5-cyanopyridine (5.84 g, 31.91 mmol), hexamethylditin (11.49 g, 35.10 mmol), lithium chloride (1.62 g, 38.29 mmol), tetrakis(triphenylphosphine)palladium (1.44 g, 1.24 mmol), 2,6-di-tert-butyl-4-methylphenol (approximately 0.01 g), and dioxane (60 mL)was heated at reflux under nitrogen for 8 hours. The resulting mixture was concentrated via evaporation under reduced pressure, and the residue was column chromatographed using silica gel (approximately 200 g) and elution with ether/hexanes [1:1] to afford the title compound (1.98 g, 7.41 mmol, 23%) as a pale yellow solid: mp, 77.0-79.0° C.; R_f=0.65 In ether/hexanes [1:1]; ^{1}H NMR ($CDCl_3$) δ 8.80 (dd, J=1.5 and 2.4 Hz, 2H), 8.03 (dd, J=1.5 and 2.1 Hz, 1H), 0.39 (s, 9H).

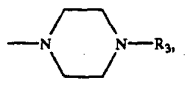
[0384] The compounds of formula I of the present invention described in the above Examples were assayed for 5-HT_{1A} and 5-HT_{1D} affinity using the aforementioned procedures with IC_{50}s of less than 0.60 μM for at least one of the above affinities.

1. A compound of the formula



I

where R_1 is of the formulae



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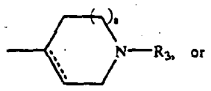
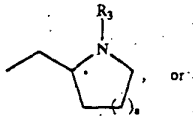


III

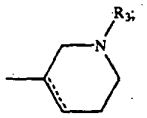
or

-continued

IV



V

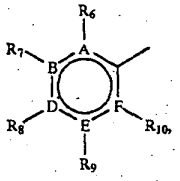


R_2 is $-R_4$, $-O-F_4$, $-O-S(O)_2-R_4$, $-NR_4R_5$, $R_4-(CH_2)_b-NH(C=X)-(CH_2)_c-$, $R_4-(CH_2)_b-O(C=O)NH-(CH_2)_c-(C=O)NH-$, $R_4-(C=O)NH-(C=O)NH-$, $-(CH_2)_b-NH(C=X)-(CH_2)_c-R_4$, $R_4-(CH_2)_b-O(C=O)-(CH_2)_c-$, $-(CH_2)_b-O(C=O)-(CH_2)_c-R_4$, $-NH(C=X)NH-R_4$, $R_4-O(C=O)O-$, $-O(C=O)NH-R_4$, $R_4-O(C=O)NH-$, $-(CH_2)_b-(C=O)-(CH_2)_c-R_4$, $-NH-S(O)_2-R_4$, $-C(OH)R_4R_5$, $-CH(OH)-R_4$, $-(C=O)-NR_4R_5$, $-CN$, $-NO_2$, substituted C_1 to C_5 alkyl, substituted or unsubstituted C_1 to C_6 alkenyl, or substituted or unsubstituted C_1 to C_6 alkynyl, said substituted moieties substituted with a moiety of the formulae $-R_4$, $-R_4R_5$, $-O-R_4$, or $-S(O)_d-R_4$;

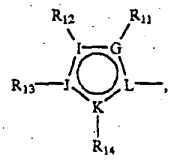
R_3 is hydrogen, $CH_3OCH_2CH_2$, C_1 to C_5 alkyl, C_1 to C_6 alkylaryl, or aryl;

R_4 and R_5 are each independently

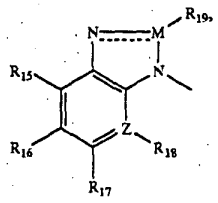
XV



XVI



XVII



hydrogen, $-CF_3$, C_1 to C_6 alkyl, C_1 to C_6 alkylaryl, with the proviso that when R_2 is $-R_4$ or $-OR_4$, R_4 is not hydrogen or C_1 to C_6 alkyl;

R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, and R_{18}, are each independently H, halogen, $-CF_3$, $-(C=O)R_{20}$, $-CN$, $-OR_{20}$, $-NR_{20}R_{21}$, $-NR_{20}SO_2R_{22}$, $-N=C-N(CH_3)_2$, $-N_{20}CO_2R_{22}$, $-S(O)R_{20}$, $-SO_2NR_2OR_{21}$, $-NO_2$, ar, C_1 to C_6 alkylaryl, $-(C=O)OR_{20}$, $-(C=O)NR_{20}R_{21}$, C_1 to C_6 alkyl, C_1 to C_6 alkenyl, and C_1 to C_6 alkynyl;

R_6 and R_7, R_7 and R_8, R_8 and R_9, R_9 and R_{10}, R_{11} and R_{12}, R_{12} and R_{13}, R_{13} and R_{14}, R_{15} and R_{16}, R_{16} and R_{17}, and R_{17} and R_{18} may be taken together to form a five-to-seven-membered alkyl ring, a six-membered aryl ring, a five to seven membered heteroalkyl ring having one heteroatom of N, O, or S, or a five-to six-membered heteroaryl ring have 1 or 2 heteroatoms of N, O, or S;

R_{19} is hydrogen or C_1 to C_3 alkyl;

R_{20} and R_{21} are each independently hydrogen, C_1 to C_6 alkyl, aryl, or C_1 to C_6 alkylaryl, or may be taken together to form a C_4 to C_7 alkyl ring;

R_{22} is C_1 to C_6 alkyl, aryl, or C_1 to C_6 alkylaryl;

A, B, D, E, and F are each independently C or N;

G, I, J, and K are each independently C, N, O, S, or (C=O), with the proviso that there is at most one of O, (C=O), or S per ring;

L and Z are each independently C or N;

M is C, N, or (C=O);

X is O or S;

a is 0, 1 or 2;

e is 0, 1 or 2;

d is 0,1, or 2;

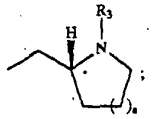
b and c are each independently 0, 1, 2, 3, 4, 5, or 6, with b+c being at most 6;

a broken line indicates the presence optionally of a double bond and the above aryl groups and the aryl moieties of the above alkylaryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C_1 to C_4 alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and C_1 to C_4 alkoxy, and pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein R_1 is formula II; R_2 is $-R_4$, $-OR_4$, $R_4-(CH_2)_b-NH(C=X)-(CH_2)_c-$, or $-(CH_2)_b-NH(C=O)-(CH_2)_c-R_4$; R_3 is hydrogen or C_1 to C_6 alkyl; R_4 is formula XV or formula XVII; A, B, D, E, and F are each independently C or N; R_6, R_7, R_8, R_9, R_{10}, R_{15}, R_{16}, R_{17}, R_{18}, and R_{19} are each independently hydrogen, halogen, $-CN$, or $-CR_{20}$; and R_{20} is C_1 to C_6 alkyl.

3. The compound of claim 1, wherein R_1 is formula III; R_2 is $-R_4$, $-OR_4$, $R_4-(CH_2)_b-NH(C=X)-(CH_2)_c-$, or $-(CH_2)_b-NH(C=O)-(CH_2)_c-R_4$; R_4 is formula XV or formula XVII; R_3 is hydrogen or C_1 to C_5 alkyl; A, B, D, E, and F are each independently C or N; Row R_6, R_7, R_8, R_9, R_{10}, R_{15}, R_{17}, R_{18}, and R_{19} are each independently hydrogen, halogen, $-CN$, or $-OR_{20}$; and R_{20} is C_1 to C_8 alkyl.

4. The compound of claim 1, wherein R_f is



R_2 is $—R_4$, $—OR_4$, $R_4—(CH_2)_b—NH(C=X)—(CH_2)—$, or $—(CH_2)_b—NH(C=O)(CH_2)_cR_4$; R_3 is hydrogen or C_1 to C_6 alkyl; R_4 is formula XV or formula XVII; A, B. D, E, and F are each independently C or N; R_6, R_7, R_8, R_9, R_{10}, R_{15}, R_{16}, R_{17}, R_{18}, and R_{19} are each independently hydrogen, halogen, —CN, or $—OR_{20}$; and R_{20} is C_1 to C_6 alkyl.

5. The compound of claim 1, wherein R_1 is formula II, formula III, or formula IV; R_2 is $—R_4$; R_3 is hydrogen or C_1 to C_6 alkyl; R_4 is formula XVII; G, I, J, and K are each independently C, N, or O; L is C; R_{11}, R_{12}, R_{13}, and R_{14} are each independently hydrogen, C_1 to C_6 alkyl, or C_1 to C_6 alkylaryl.

6. The compound of claim 1, said compound being selected from:

7-(Imidazolo[4,5-b]pyridin-1-yl)-1-(1-methylpyrrolidin-3-yl)naphthalene;

7-(4-Chlorobenzamido)-1-(pyrrolidin-2-(R)-ylmethyl) naphthalene;

2-[8(4-Methylpiperazin-1-yl)naphthalen-2-yloxy]nicotinonitrile;

1 -(Methylpiperazin-1-yl)-7-pyrimidin-5-yl)naphthalene;

7-(5-Cyanopyridinyyl)-1-(4-methylpiperazin-1-yl)naphthalene;

1 -(Piperazin-1-yl)-7-(pyrimidin-5yl)naphthalene;

7-(4-Chlorobenzamido-1-(4-methylpiperazin-1-yl)naphthalene;

7-(3-Methoxyphenyl) 1 -(4methylpiperazin-1-yl)naphthalene;

7-(Imidazolo[4,5-b]pyridin-1-yl)-1-(4-methylpiperazin-1-yl)naphthalene;

8-(4-Methylpiperazin-1-yl)naphthalene-2-carboxylic acid 4-chlorobenzylamide;

7-(4-Methoxyphenyl)-1-(4-methylpiperazin-1-yl)-naphthalene;

7-Pyrimidin-2-yloxy-1-(4-methylpiperazin-1-yl)naphthalene;

7-(Benzimidazol-1-yl)-1-(4methylpiperazin-1-yl)naphthalene; and

8-(1-Methylpiperidinryl)naphthalene-2-carboxylic acid 4-chlorobenzylamide.

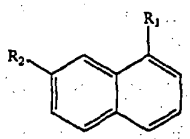
7. A pharmaceutical composition for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain, Alzheimer's disease, and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising an amount of a compound according to claim 1 effective in treating such condition and a pharmaceutically acceptable carrier.

8. A pharmaceutical composition for treating disorders arising from deficient serotonergic neurotransmission comprising an amount of a compound according to claim 1 effective in treating such condition and a pharmaceutically acceptable carrier.

9. A method for treating a condition selected from hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, Alzheimer's disease, pain and chronic paroxysmal hemicrania and headache associated with vascular disorders comprising administering to a mammal requiring such treatment an amount of a compound according to claim 1 effective in treating such condition.

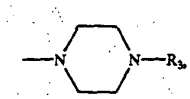
10. A method for treating disorders arising from deficient serotonergic neurotransmission comprising administering to a mammal requiring such treatment an amount of a compound according to claim 1 effective in treating such condition.

11. A compound of the formula



I

where R_1 is of the formulae



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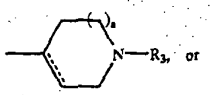
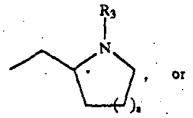
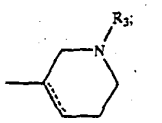


III



IV



V

R_2 is $(Methyl)_3Sn—$ or $(Butyl)_3Sn—$; R_3 is hydrogen, C_1 to C_6 alkyl, C_1 to C_6 alkylaryl, or aryl; a is 0, 1, or 2; and a broken line indicates the presence optionally of a double bond and the above aryl groups and the aryl moieties of the above alkylaryl groups are independently selected from phenyl and substituted phenyl, wherein said substituted phenyl may be substituted with one to three groups selected from C_1 to C_4 alkyl, halogen, hydroxy, cyano, carboxamido, nitro, and C_1 to C_4 alkoxy.

* * * * *